Design, synthesis, and evaluation of new chemosensitizers in multi-drug-resistant Plasmodium falciparum.

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A series of new chemosensitizers (modulators) against chloroquine-resistant Plasmodium falciparum were designed and synthesized in an attempt to fabricate modulators with enhancing drug-resistant reversing efficacy and minimal side effects. Four aromatic amine ring systems-phenothiazine, iminodibenzyl, iminostilbene, and diphenylamine-were examined. Various tertiary amino groups including either noncyclic or cyclic aliphatic amines were introduced to explore the steric tolerance at the end of the side chain. The new compounds showed better drug-resistant reversing activity in chloroquine-resistant than in mefloquine-resistant cell lines and were generally more effective against chloroquine-resistant P. falciparum isolates from Southeast Asian (W2 and TM91C235) than those from South America (PC49 and RCS). Structure-activity relationship studies revealed that elongation of the alkyl side chain of the molecule retained the chemosensitizing activity, and analogues with four-carbon side chains showed superior activity. Furthermore, new modulators with phenothiazine ring exhibited the best chemosensitizing activity among the four different ring systems examined. Terminal amino function has limited steric tolerance as evidenced by the dramatic lose of the modulating activity, when the size o substituent at the amino group increases. The best new modulator synthesized in this study possesses all three optimized structural features, which consist of a phenothiazine ring and a pyrrolidinyl group joined by a four-carbon alkyl bridge. The fractional inhibitory concentration (FIC) index of the best compound is 0.21, which is superior to that of verapamil (0.51), one of the best-known multi-drug-resistant reversing agents. Some of the analogues displayed moderate intrinsic in vitro antimalarial activity against a W-2 clone of P. falciparum.

PMID: 12061877 [PubMed - indexed for MEDLINE]

☐ **2:** Southeast Asian J Trop Med Public Health 1987 Jun;18(2):253-8

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Flunarizine and verapamil inhibit chloroquine-resistant Plasmodium falciparum growth in vitro.

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Using pharmacological properties in relation to the biochemistry of P. falciparum, verapamil, flunarizine, and chlorpromazine which are calcium blockers were selected to test for their antimalarial activity against P. falciparum in vitro. Results revealed that the drugs inhibited parasite population growth in the following order of IC50: verapamil 1 X 10(-6) M, chlorpromazine 3.5 X 10(-6) M, and flunarizine 5 X 10(-6) M. These three calcium blockers have antimalarial effects on chloroquine resistant parasite (alone T9/94) but are less potent when compared with the efficacy of quinine or mefloquine in vitro.

PMID: 3313742 [PubMed - indexed for MEDLINE]

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Epidemiology of drug-resistant malaria.

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Since the first reports of chloroquine-resistant falciparum malaria in southeast Asia and South America almost half a century ago, drug-resistant malaria has posed a major problem in malaria control. By the late 1980s, resistance to sulfadoxine-pyrimethamine and to mefloquine was also prevalent on the Thai-Cambodian and Thai-Myanmar (Thai-Burmese) borders, rendering them established multidrug-resistant (MDR) areas. Chloroquine resistance spread across Africa during the 1980s, and severe resistance is especially found in east Africa. As a result, more than ten African countries have switched their first-line drug to sulfadoxine-pyrimethamine. Of great concern is the fact that the efficacy of this drug in Africa is progressively deteriorating, especially in foci in east Africa, which are classified as emerging MDR areas. Urgent efforts are needed to lengthen the lifespan of sulfadoxine-pyrimethamine and to identify effective, affordable, alternative antimalarial regimens. Molecular markers for antimalarial resistance have been identified, including pfcrt polymorphisms associated with chloroquine resistance and dhfr and dhps polymorphisms associated with sulfadoxine-pyrimethamine resistance. Polymorphisms in pfmdr1 may also be associated with resistance to chloroquine, mefloquine, quinine, and artemisinin. Use of such genetic information for the early detection of resistance foci and future monitoring of drug-resistant malaria is a potentially useful epidemiological tool, in conjunction with the conventional in-vivo and in-vitro drug-sensitivity assessments. This review describes the various features of drug resistance in Plasmodium falciparum, including its determinants, current status in diverse geographical areas, molecular markers, and their implications.

Publication Types:
- Review
- Review, Tutorial

PMID: 11937421 [PubMed - indexed for MEDLINE]

14: Trans R Soc Trop Med Hyg 2001 Nov-Dec;95(6):661-7

A randomized controlled trial on the efficacy of alternative treatment regimens for uncomplicated falciparum malaria in a multidrug-resistant falciparum area of Bangladesh--narrowing the options for the National Malaria Control Programme?

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We performed an open, randomized chemotherapy trial comparing the recommended first-, second- and third-line drug regimens, as well as mefloquine, for uncomplicated falciparum malaria in Bangladesh in 1996-97. The regimens were chloroquine for 3 days (CQ, Group I), quinine sulphate for 3 days followed by single-dose sulfadoxine-pyrimethamine (Q3 + SP, Group II), quinine for 7 days (Q7, Group III), and mefloquine 20 mg/kg single dose (MEF, Group IV). Subjects were symptomatic patients, aged > or = 12 years, with parasite density 500-250,000/mm3 and no history of taking antimalarials during the previous week. Drug administration was supervised and subjects were followed clinically and with blood slides in the hospital for 8 days, then as outpatients on days 14, 21 and 28. A total of 413 subjects (149, 145, 49 and 70 in Groups I-IV, respectively) completed the study. Early treatment failures (persistent or worsening clinical manifestations by day 3 confirmed with parasitological examinations) occurred only in the chloroquine group. RII and RIII parasitological failures occurred in 56%, 12%, 8% and 14% in Group I-IV, respectively. There were significantly more clinical and parasitological failures with chloroquine than with Q3 + SP, which we now recommend as a better (but far from ideal) choice for first-line therapy. The alternative compounds show parasitogical evidence of Plasmodium falciparum resistance. Further studies are needed to determine the optimum treatment for malaria in Bangladesh.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 11816441 [PubMed - indexed for MEDLINE]

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11: Clin Infect Dis 2001 Dec 15;33(12):2009-16 Related Articles, Books, LinkOut

The University of Chicago Press

Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum.

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The emergence and spread of multidrug-resistant Plasmodium falciparum compromises the treatment of malaria, especially during pregnancy, where the choice of antimalarials is already limited. Artesunate (n=528) or artemether (n=11) was used to treat 539 episodes of acute P. falciparum malaria in 461 pregnant women, including 44 first-trimester episodes. Most patients (310 [57.5%]) received re-treatments after earlier treatment with quinine or mefloquine. By use of survival analysis, the cumulative artemisinin failure rate for primary infections was 6.6% (95% confidence interval, 1.0-12.3), compared with the re-treatment failure rate of 21.7% (95% confidence interval, 15.4-28.0; P=.004). The artemisinins were well tolerated with no evidence of adverse effects. Birth outcomes did not differ significantly to community rates for abortion, stillbirth, congenital abnormality, and mean gestation at delivery. These results are reassuring, but further information about the safety of these valuable antimalarials in pregnancy is needed.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial

PMID: 11712093 [PubMed - indexed for MEDLINE]

13: J Postgrad Med 2001 Jan-Mar;47(1):24-6

JPGM

Severe acute renal failure in malaria.

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BACKGROUND: We have noticed a recent rise in the incidence and severity of acute renal failure (ARF) in malaria. AIM: To study the incidence, severity and outcome of ARF in malaria. SETTING and DESIGN: It is a retrospective analysis of data of one year from a tertiary medical centre in a metropolitan city. MATERIALS AND METHODS: Patients with ARF and smear positive malaria were evaluated. STATISTICAL ANALYSIS: Results were expressed as mean, range and standard deviation. RESULTS: Out of 402 detected smear positive malaria, 24 had ARF. Eighteen were of the age group 21-40 years. Plasmodium falciparum (PF) was detected in 16, Plasmodium vivax in three, and mixed infection in five. Non-oliguric ARF was seen in 14. Eighteen showed severe ARF (Serum creatinine >5 mg%). Twenty-two patients needed dialysis. Prolonged ARF lasting for 2-6 weeks was seen in eight. Seventeen patients recovered completely, while seven showed fatal combination of disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), severe ARF and PF malaria. No response was seen to chloroquine and artesunate given alone and twenty patients required quinine. CONCLUSION: ARF necessitating dialysis was seen in 92% of patients with ARF in malaria. PF infection, severe ARF, DIC and ARDS were poor prognostic factors. Resistance was noted to both chloroquine and artesunate.

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